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Pharmacognosy in the New Millennium: Leadfinding and Biotechnology

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Pharmacognosy was defined as a pharmaceutical discipline for the first time in 1815 by Seidler (Tschirch 1909). Tschirch gave the following definition (translated from the German): "With the name Pharmacognosy we mean the science which has the task to learn everything about drugs originating from plants or animals in all aspects, except the physiological effect, to describe them correctly and under a general vision connect this knowledge". During the 19th century it was by far the most important pharmaceutical discipline, the mother of all present day pharmaceutical disciplines. However, 100 years ago (1899) the first signs of a new era became obvious with the introduction of a very successful synthetic drug—aspirin (Viktorin 1999), which was the first example of using nature as a lead for a new synthetic drug. Despite some obvious failures, such as heroin, gradually synthetic chemistry became more important for developing new drugs. The wish to have pharmaceutical formulations containing single pure compounds with well defined activities was an important driving force behind this trend.

Pharmacognosists have always been very keen to introduce new technologies into their discipline. In the 19th century microscopy was introduced for the quality control of pharmaceutical preparations from plants. However, for too many years pharmacognosy stayed with these methods, and with the rapidly decreasing number of herbal preparations in the pharmacy, the discipline had great difficulty in holding its prominent position in the pharmaceutical curriculum in the 1960s and 1970s. Fortunately, some visionary pharmacognosists were able to open up new directions. The development of thin-layer chromatography by the well-known pharmacognosist Professor Egon Stahl is probably the best example (Stahl 1967). Also in the field of gas chromatography and high-performance liquid chromatography (HPLC), pharmacognosists were among the pioneers in the analysis of plant materials. For studies of the active compounds in plants, these chromatographic methods became important tools. Moreover, in the 1970s spectrometric methods such as mass spectrometry (MS) and nuclear magnetic resonance (NMR) became commonplace for the pharmacognosists in their search for new biologically active compounds in plants. However, in that period developing new drugs from plants was not as easy as development of synthetic drugs, as the pharmacological test systems (mainly in-vivo animal experiments and in-vitro isolated organs) are not suited for bioassay-guided fractionation of active compounds from plant extracts. This requires methods that can readily measure large numbers of samples in a short time. Natural products only remained a major source for new drugs for activities for which simple test methods were available. This is clearly illustrated by the fact that most antibiotics and antitumour drugs are natural products (Cragg et al 1997). These activities can be easily tested in in-vitro systems based on cell cultures. From 1983 to 1994, of all new approved drugs, 78% of new antibiotics and 61% of new antitumour drugs were natural products or derived from natural products.

Currently, there is a rapidly increasing interest in pharmacognosy and natural product research. The number of new international scientific journals in the field illustrates this trend. The increasing interest has also been clearly reflected in a meeting of the four major international societies in the field of pharmacognosy and natural product research. This joint meeting, a 5-yearly event, took place most recently in July 1999 and attracted more than 1100 scientists from all over the world to Amsterdam, the largest number ever in this field and almost double the number attending the previous meeting.

There are several reasons which may explain the increased interest in natural products and pharmacognosy: the search for new leads for drug development; the need for biotechnology for the production of pharmaceuticals; health claims for food (nutraceuticals); validation of traditional medicines; and increased interest in phytotherapy.

With this development in the past decade, we can now distinguish three major areas of interest for the pharmacognosist: studies of new biologically active natural products; production of drugs from natural

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sources, including new methods such as biotechnology; and quality control of drugs from natural sources. The first two aspects I should like to discuss in more detail. The studies for new active compounds have two major goals: finding new leads for drug development and studies on the validation of traditional medicines. Traditionally pharmacognosists have focused on plants as the source for new compounds, whereas work on microorganisms has mostly been in the hands of industrial or academic chemistry groups. Here I too will mainly deal with plants.

Leadfinding

Nature is an almost infinite resource for drug development. The number of organisms that exist in the world is not so easy to assess. Pimm et al (1995) made an effort to express biodiversity in numbers, estimating the total number of species to be 10–100 million. The greatest diversity is within insects (the number of arthropod species estimated to be as high as 30 million), algae, prokaryotes and fungi (each about 1·5 million species). Plants comprise a relatively small group with about 250 000 species, of which approximately 6% has been studied for biological activity, and about 15% has been studied phytochemically (Verpoorte 1998). All of these organisms produce a number of secondary metabolites which are involved in the interaction of the organism with its environment. During evolution this has resulted in a large chemodiversity (Harborne 1978).

What are these secondary metabolites? The number presently known is about 139 000. Each year about 4000 new structures are reported. NAPRALERT and the Dictionary of Natural Products (1999) are the two main databases for natural products (Corley & Durley 1994). NAPRALERT collects and abstracts all papers on natural products and their biological activity, as well as ethnopharmacological data. The Dictionary of Natural Products (Chapman & Hall 1999) is a compilation of all known compounds and now has about 139 000 entries. As can be seen in Table 1, the major group is that of the terpenoids, the second largest group is that of the alkaloids. The latter group, in particular, contains a large number of medicines. This is due to their special characteristic of being water-soluble compounds under acidic conditions and having lipophilic properties under neutral and basic conditions. In fact, quite a large proportion of all medicines contain a tertiary nitrogen.

Despite enormous structural diversity, nature only uses a few basic building blocks (Luckner 1990; Verpoorte & Alfermann 1999). These are acetate (C_2), isoprenoid (C_5) and phenylpropanoid (C_9) units. The acetate unit is used in polyketide biosynthesis, particularly well developed in microorganisms. The isoprenoid pathways leads to all terpenoids by coupling two or more C_5 units. Terpenoids are found in all organisms. The phenylpropanoid pathway is most typical for plants; it is based on phenylalanine and tyrosine and, via cinnamic acid, this pathway leads to lignin and lignans among others. In combination with three acetate units the C_9 unit leads to the flavonoids and the anthocyanins, well known for their role in the colouring of flowers. With the building blocks mentioned, and some amino acids, most organisms make more or less similar basic structures. The diversity results from various "decorating" enzymes found in each species, that introduce new functionalities, such as hydroxy, epoxy and methoxy groups. Oxidation (cytochrome P450 enzymes, peroxidases and dioxygenases) and reduction are the most common reactions. Biological activity is sometimes altered by the addition of one or more sugar molecules to the basic structure. In fact, the trend for combinatorial chemistry of synthetic organic chemists is nothing new, it is as old as evolution. Combinatorial chemistry has even been called the chemists surrogate for the rain forest (Hogan 1997).

Table 1. Number of secondary metabolites from all organisms as present in the Dictionary of Natural Products (Chapman & Hall 1999).

Total number of entries: 139 000, including:	
Aliphatics	5950
Polyketides	2753
Carbohydrates	3397
Oxygen heterocycles	1484
Simple aromatics	5041
Benzofuranoids	444
Benzopyranoids	2859
Flavonoids	8405
Tannins	783
Lignans	1729
Polycyclic aromatics	2621
Terpenoids	30 500
hemi-	58
mono-	2243
sesqui-	10 358
di-	8343
ses-	421
tri-	7210
tetra-	638
poly-	54
steroids	4600
Amino acids, peptides	4303
Alkaloids	16 833
indole	3874
isoquinoline	3243
steroidal	925

For exploring nature's chemodiversty, the situation has been changed dramatically in recent years by the introduction of high-throughput screening (HTS) methods (for several reviews see Bohlin & Bruhn 1999). By using molecular targets, a large number of samples (up to 100 000 in 24 h) can be screened for a single activity. Obviously, synthetic chemists are not able to produce such numbers of new compounds. Their answer was the development of combinatorial chemistry and testing mixtures of compounds obtained through novel solid-phase chemical synthetic methods. About 10 years ago a typical synthetic chemist in the pharmaceutical industry made about 8 new chemical entities (NCEs) per year; in the near future this number is expected to reach 50 per year (Valkema 1999). However, the structural diversity arising from synthetic chemistry will never match nature; a novel active compound like paclitaxel, having 11 asymmetric carbons, will never be designed in a synthetic laboratory.

Thus HTS offers new possibilities for developing drugs from natural products. It allows rapid screening of large numbers of extracts and it is very suitable for bioassay-guided fractionation, which in the past was the major bottleneck in studies of active compounds in plant extracts. Powerful chromatographic methods in combination with HTS are now very efficient ways to new leads for drug development. A project sponsored by Astra, in which the Australian biodiversity is screened for new leads, is a successful example of this new approach (Quinn 1999). In the coming years, technological developments will further improve the rate at which new active compounds can be isolated and identified from natural sources. Recently HPLC on-line methods have been developed for determining biological activity (Oosterkamp et al 1997a, b). We have, for example, developed such a method for the detection of acetylcholinesterase inhibition in plant extracts (Ingkaninan et al, unpublished results). By using prefractionation methods, the chances of finding novel compounds will be increased and dereplication, the rapid identification of known active compounds or false positives, will take up less time.

The availability of sources of biodiversity, however, is presently a major limiting-factor. The largest number of species is in second and third world countries which, in most cases, do not have the resources for conducting an extensive screening of their national biodiversity. On the other hand, negotiations over revenues with pharmaceutical companies interested in screening the biodiversity are not easy because of the difficulty in defining the value of making biodiversity available for screening. Compared with the total process of drug development, the costs of leadfinding are only a relatively small part of the total budget. So despite the good intentions of various international treaties and the Manilla declaration concerning the right of each country to its biodiversity (Baker et al 1995), presently establishing collaborations between industry, academia and governments concerning exploration of biodiversity might be a difficult task. The fact that biodiversity does not heed political borders does not ease this process.

Plant cell culture extracts are an interesting option for screening, as they are easy to scale-up when an interesting activity is found (McAlpine et al 1999). Moreover, plant cell cultures can be made from rare plants to ensure the production of compounds from those plants which have shown interesting activity.

Besides the more or less random screening of organisms for biological activity, one can also look at ecological leads for biological activity (Verpoorte 1998, 1999). For example, young leaves and seedlings are expected to be more strongly protected against predators by, among other factors, secondary metabolites, than older parts of a plant. For example, we found very high levels of quinoline alkaloids (quinine and related compounds) in seedlings of *Cinchona* (Aerts et al 1990, 1991a, b) and we detected the highest level of ginkgolides ever found, in seedlings of *Ginkgo biloba* (Carrier et al 1998).

A very different approach to leadfinding is from the study of traditional medicines. Such studies can serve two goals: validation of the use of traditional medicines and finding new leads. With the increased awareness of developing countries that their cultural heritage is a great treasure, studies of traditional medicine are receiving more attention. They can lead to an efficient use of such preparations, avoiding the need to import expensive western medicines. Moreover, availability directly from the field is a major advantage in remote areas. In fact, it is estimated that about 80% of the world population relies on traditional medicines in primary health care (Baker et al 1995). Such studies should not only concern activity, but also toxicity. Compounds responsible for activity in traditional medicines do not necessarily lead to new drugs. In many cases compounds might already be known, or compounds might not perform better than already known drugs. HTS is within the field of industrial research, while traditional medicine is mainly studied by academic institutions and government laboratories. In Table 2 the different approaches are summarized.

Biotechnology

Another area which has opened up new perspectives in pharmacognosy is biotechnology. Traditionally pharmacognosy focuses on plants and relatively little attention has been paid in both teaching and research to microorganisms as a source of drugs. The classical biotechnology in the production of, for example, antibiotics has been more or less outside the scope of the discipline. However, when plant cell biotechnology emerged as a new possibility for the production of plant secondary metabolites in the mid 1970s, the pharmacognosists eagerly moved into this field. The aim was the production of known pharmaceuticals by means of plant cell cultures. In the past two decades such production of plant-derived pharmaceuticals has been extensively studied by a number of groups all over the world. Besides the enormous possibilities of biotechnological production of pharmaceuticals using microbial, plant, insect or mammalian cells, biotechnology also offers genetic engineering as an important new technology. Genetic engineering can be used not only to increase yields in an organism producing valuable pharmaceuticals, but also to introduce the production of valuable compounds in other production organisms. For example, one can produce pharmaceutical proteins in microorganisms (such as insulin in *Escherichia coli*) or plants (such as human serum albumin or vaccines) (Pen et al 1993; Ponstein et al 1996; Arntzen 1997; Cunningham & Porter 1998). In Table 3, various aims in biotechnology and the possible role of the pharmacognosists (pharmacists) are summarized. Below, some of these aspects for plant cell biotechnology and genetic engineering from a pharmaceutical (pharmacognostical) point of view will be discussed in more detail.

Plant cell biotechnological production

For the biotechnological production of complex natural products, plant cell cultures are an interesting option. A cell culture can be obtained from any plant species. In such a culture each cell has all the genes necessary for all the functions of a plant, including secondary metabolism (totipotency). For the application of such in-vitro cultured cells in commercial production there are two major questions to be answered: is the technology feasible, and is the economy of the process competitive?

The first point was considered as a major constraint. Shear forces in stirred bioreactors were thought to be a major problem for large vacuolated plant cells. Some studies in the 1970s claimed that plant cells grew better and had a higher production of secondary metabolites in low-shear bioreactors (such as airlift reactors) than in stirred-tank bioreactors. However, more recent studies (Scragg et al 1986; Meijer et al 1987) showed that plant cells are not very shear sensitive and can easily be grown in stirred bioreactors. The feasibility of the technology has been confirmed by reports on the large-scale culture of plant cells in bioreactors (e.g. in stirred tanks of $60\,m^3$ working volume; Westphal 1990). Cost-price calculations for products from plant cell biotechnology-based process have been made by several authors (Goldstein et al 1980; Fowler & Stepan-Sarkissian 1983; Drapeau et al 1987; Van Gulik et al 1988; Verpoorte et al 1991; 1993). We have calculated that a typical production of $0{\cdot}3\,g\,L^{-1}$ in 14 days results in a price of $\$1500\,kg^{-1}$. A ten-fold improvement of the productivity results in a price of $\$430\,kg^{-1}$ (Van Gulik et al 1988; Verpoorte et al 1991). The most important cost factor is the investments in the bioreactors. Media costs are only about 5% of the costs in the first example, and 20% in the second. Depreciation of the large bioreactor facilities con-

Table 2. Different approaches for finding new biologically active natural products (leads) for drug development.

Selection materials	Type of screening	Advantages	Problems
At random	HTS	Large numbers of species are available	Procurement of all samples
Ecology based	HTS	Increased chance of finding certain type of activities	Little knowledge about ecology available
	Phytoalexins: Antimicrobial Antitumour Insecticidal		
Traditional use	Double blind studies	Increased chance of finding active compounds	Intellectual property rights
	In-vivo In-vitro isolated organs		
	On activity-based selected targets	Validation of use of traditional medicines	

Table 3. Role of the pharmacognosist in pharmaceutical biotechnology.

Aim	Possible role in pharmacognosy	In collaboration with	Methods
Production of Macromolecules (e.g. proteins, antibodies, enzymes) Microorganisms Animal cells Animals Insect cells Plant cells Plants	Quality control Process Products	Biochemical engineers	Analysis DNA/RNA (e.g. PCR) Protein characterization (e.g. electrophoresis, LC-MS)
Production of low molecular weight compounds Microorganisms Plant cells Plants	Quality control Process Product	Biochemical engineers	Chromatography, NMR
Improving production of low molecular weight compounds	Epigenetic modifications	Biochemical engineers	Cell culture methods
	Biosynthetic pathway mapping		Genomics, proteomics, metabolomics, phytochemistry, enzymology, molecular biology
	Genetic engineering pathways	Molecular biologists	
Generating new compounds	Genetic engineering pathways	Molecular biologists	Molecular biology
Functional food, nutraceuticals	Identification of active compounds Biosynthesis mapping	Pharmacologists,	Phytochemistry, enzymology Genomics, proteomics, metabolomics, phytochemistry, enzymology, molecular biology
	Genetic engineering pathways	Toxicologists Molecular biologists	Molecular biology, pharmacology, toxicology
Gene therapy	Quality control Process Product	Molecular biologists	Molecular biology

tributes to the majority of the cost. The lower yield-level used for these calculations is, for example, achieved in the production of ajmalicine in *Catharanthus roseus* cell cultures (for reviews see Van der Heijden & Verpoorte 1989; Moreno et al 1995). The 10-fold higher yield has been achieved for berberine in *Coptis japonica* cell cultures, which are capable of even higher levels: up to $7\,g\,L^{-1}$, the highest production in plant cells ever reported (Sato et al 1982; Sato & Yamada 1984; Fuyita & Tabata 1987). The productivity for antibiotics such as penicillin in cultures of microorganisms can be as high as $30–50\,g\,L^{-1}$. There is no theoretical reason why plant cells should produce less. This statement can be illustrated by production of secondary metabolites of 20–60% of the dry weight of plant tissue or plant cells. Such examples are the production of tannins and proanthocyanidins in callus cultures of *Pseudotsuga menziesii* (Zaprometov 1988a, b) and anthraquinones in *Rubia fruticosa* cell cultures (Schulte et al 1984). Plant cells are thus capable of diverting a large part of their metabolic flux into secondary metabolism.

Some commercial successes have been achieved, such as the production of shikonin (Fuyita & Tabata 1987), the production of ginseng roots biomass and some polysaccharide preparations (Fu et al 1999; Hibion & Ushiyama 1999). However, for the most interesting compounds such as hyoscyamine, morphine, quinine and vinblastine, the productivity was too low, or even zero (Verpoorte et al 1991; 1993). Studies to improve yields first focused on selection of high-producing cell lines and epigenetic manipulation. As this, in most cases, did not result in the necessary increase in yields for commercialization, research moved into new directions, such as the culture of differentiated cells, induction of secondary metabolites by means of elicitors and the use of immobilized cells. However, for the compounds of interest, none of these approaches has so far resulted in commercially viable processes.

Products that came close to a succesful industrial process were rosmarinic acid and sanguinarine. But as these compounds did not reach the market, interest in the processes also waned from an industrial point of view. A successful process was developed for taxol, for which a productivity increase of 10–20-fold was achieved compared with the average *Taxus* cultures (for reviews see Fu

et al 1999). However, the product of such a process then requires official approval by registration authorities as a raw material for the production of pharmaceuticals.

Plant cell cultures may play an important role during the development of new drugs from plants. Plant cells may provide the required amount of a compound during its development, when an agricultural or horticultural production is not yet available. In those cases in which agriculture does not work, plant cell biotechnology might be the final production method.

In the meantime, plant cell cultures have developed into an excellent tool for the study of the biosynthesis of secondary metabolites and for the cloning of genes involved in such pathways (Zenk 1991, 1995; Hashimoto & Yamada 1994; Verpoorte et al 1998; 1999). These genes can be used for genetic modification of plants or plant cell cultures for improving productivity (see below) (Hashimoto & Yamada 1994; Kutchan 1995; Verpoorte & Alfermann 1999).

Genetic engineering

Proteins. Nowadays, in principle new genes can be introduced into any organism. This means that, for the production of certain valuable pharmaceuticals such as proteins, one can cross the borders between species; any type of organism can be considered for the production of pharmaceutical proteins. Post-translational modifications of proteins are an important aspect in choosing the production organism. Plants and plant cells are, like mammalian cells, capable of protein glycosidylations and should thus be attractive production systems (Kusnadi et al 1997). However, in the case of products used parenterally, proving the safety of the product from such a source will be an important limitation for the production of mammalian proteins in plants. Despite the fact that plants would be by far the cheapest source, safety requirements would impose quite extensive toxicological studies, comparable with those required in the development of a completely new drug. Human serum albumin (HSA) can be mentioned as an example (Pen et al 1993). Without any difficulty one can produce this in plants expressing the gene encoding HSA. Chemically, the protein thus formed is identical to the human protein. However, purification and subsequent studies necessary to prove its safety hamper further application. This means that for such proteins one will stay with the production methods generally considered to be safe. Production in plants is of interest only for special products. For example, the production of oral vaccines by means of genetically engineered edible plants (such as bananas) is being developed as a cheap way to help vaccination programmes in third-world countries (Shahidi et al 1999). The main restriction for this is that most vaccines do not work orally. A much more promising and revolutionary application is the production of antibodies in plants (Conrad & Fiedler 1994; Ma & Hein 1996; Whitelam & Cockburn 1996; Cunningham & Porter 1998). It opens the way for the production of antibodies for a very low price, with the potential for all kinds of new applications (e.g., the use of such antibodies in caries prevention).

Low molecular weight compounds. Genetic engineering can also be applied to improve the yield of low molecular weight compounds in the producing organisms (e.g. penicillin). I will briefly give some examples of genetic engineering concerning plant-derived pharmaceuticals. Three possibilities (discussed below) can be envisaged: increasing the production of a compound in plant or plant cell culture; producing a plant compound in a micro-organism; and production of a new compound in a plant or plant cell culture.

The production of secondary metabolites can be regulated in different ways: the flux towards the compound might be regulated through the activity of enzymes involved, or by feedback inhibition. The carbon flux may be diverted into competitive pathways. The product level may also be affected by catabolism of the secondary metabolite (Dagnino et al 1994; Dos Santos et al 1994; Schripsema et al 1994). Competitive pathways and catabolism can be blocked by introducing antisense genes for the genes encoding the enzymes concerned.

By identifying possible limiting steps in biosynthetic pathways, one can subsequently clone the gene encoding the enzyme involved and over-express this enzyme or use genes from other sources to overcome the limitation. We have shown that it is feasible to over-express tryptophan decarboxylase and strictosidine synthase, two important genes from the terpenoid indole alkaloids, in cell cultures of various plants. In *Catharanthus roseus* cell cultures, the over-expression of these endogenous genes leads to increased levels of enzyme activity, but increase in the alkaloid production was observed only with the latter gene (Goddijn et al 1995; Canel et al 1998). Expression in tobacco cells results in the production of tryptamine (Hallard et al 1997; Leech et al 1998 and, after feeding secologanin, also in the production of strictosidine (Hallard et al 1997). This shows that it is feasible to engineer secondary-metabolite pathways of pharmaceutically important compounds, although the increases mainly concern the immediate product of the over-expressed enzyme. A promising option is

the cloning of regulatory genes of a particular pathway and over-expression of these genes (Lloyd et al 1992; Martin 1996; Grotewold et al 1998).

Genes from a plant can be expressed in microorganisms. The production of a plant secondary metabolite in a microorganism, however, requires the availability of the necessary precursors. As most secondary metabolites are the result of a large number of steps, this approach is thus limited to products which only need a few steps starting from an available precursor, otherwise one needs to add the necessary precursors. This only makes sense if these are readily available for a low price. A recent patent application we made concerns an example of such an approach (Geerlings et al 1998). Strictosidine synthase and strictosidine glucosidase were expressed into yeast. Growing this transgenic yeast on the juice of the berries of *Symphoricarpus albus*, containing both the sugar for the growth of the yeast and secologanin for the production of indole alkaloids, $2\,g\,L^{-1}$ of alkaloid could be produced. Adding further steps of the alkaloid biosynthetic pathways may eventually lead to the production of known commercially important alkaloids such as ajmalicine or quinine.

Recent years have seen the development of new possibilities for increasing chemodiversity. Recombinatorial biochemistry, also called combinatorial biochemistry, particularly can be mentioned in this context. It concerns the expression of genes in other organisms, thus affecting the biosynthesis of secondary metabolites. Engineering polyketide bioynthesis in microorganisms leading to the production of new antibiotics is an excellent example of this (Madduri et al 1998; Salas & Mendez 1998). This approach is now also being probed in plants.

An example of opening a new pathway in a plant is the production of salicylic acid (Verberne et al 1998, 1999). Salicylic acid is an important signal compound in systemic acquired resistance in plants. The biosynthesis of salicylic acid is thought to occur via cinnamic acid, though the pathway has not yet been completely elucidated. In microorganisms, salicylic acid is produced via isochorismate from chorismate, an abundant precursor in plants and microorganisms for the production of phenylalanine/tyrosine and tryptophan. By introduction of genes from microorganisms (*entC* and *orfd* encoding, respectively, isochorismate synthase and isochorismate pyruvate lyase, combined with the signal sequence for chloroplast targeting from the small subunit of Rubisco and the 35*S* promoter) into plants, we have achieved constitutive production of salicylic acid in plants. The transgenic plants show high salicylic acid levels which are correlated with a decrease in necrosis after infection with tobacco mosaic virus. Other examples are the introduction of the gene encoding stilbene synthase into various plants, resulting in the production of the phytoalexin and antioxidant resveratrol (Hain et al 1990, 1993) and the introduction of the gene encoding hyoscyamine 6-hydroxylase in *Atropa belladonna*, resulting in the production of scopolamine instead of hyoscyamine (Yun et al 1992; Hashimoto & Yamada 1994). This proof of principle invites further applications of this exciting technology.

Conclusions

From this very brief historical picture, and a short review of some aspects of the present day research, it is clear that pharmacognosy has entered a completely new era. Its role in the quality control of herbal drugs has decreased, but this remains a very important task, which may help to avoid mistakes as has occurred, for example, in Belgium where wrong ingredients were used in a herbal slimming preparation, causing severe kidney damage in a number of people. The trend wherein some European governments want to ban phytotherapy from the health-care system, carries the risk that such disasters will happen again. All phytotherapy should be in the hands of professionals capable of assuring a proper quality control.

In terms of drug development and production, there are numerous new possibilities for the pharmacognosist. Leadfinding for drug development using biodiversity or traditional medicines is one major area in which one can see a rapidly increasing activity. The other area is that of biotechnology. In terms of the professional situation, quality control is an important aspect of this field, and pharmacognosy can play an important role. This includes, among other applications, the quality control of proteins and also in gene therapy, wherein lies a challenging task for future pharmacists. In terms of research, important new possibilities lie mostly in the production by means of plant cell and tissue culture and metabolic engineering, for increasing the production of natural products or even producing completely new ones.

These new technologies also require, of course, a new type of pharmacist and pharmacognosist. A pharmacognosist should not only have expertise in the botanical aspects of medicinal plants, but also in phytochemistry, advanced seperation methods, proteins and molecular biology. The latter two areas particularly, are new to the discipline of pharmacognosy. In the field of proteins, proteomics would fit nicely into the expertise of pharmacog-

nosists. Molecular biology techniques would be important tools not only in the quality control of biotechnological products, but also in the characterization of medicinal plants. Vegetative contamination in material obtained from plants could probably be found at very low levels using the polymerase chain reaction (PCR). DNA-chips open further exciting opportunities, for example, for studying the effect of medicinal plants one can use proteomics and DNA-chips for comparing changes in expression levels of genes and the resulting effects on protein levels. This might be much more sensitive than the present-day pharmacological assays and also might detect multiple changes.

We have exciting times ahead. There are many options for the pharmacognosist, but making choices is necessary—we cannot do all. Finally, despite the enormous potential of new technologies, one should not make the mistake of making a molecular biologist out of a pharmacist. That would be as deadly for the discipline as microscopy was for the pharmacognosists. The future is in collaboration between experts: multidisciplinary teams solving scientific (e.g. biological) problems together, rather than monodisciplinary approaches, making drugs of the future by biotechnology, or finding new ones through bioprospecting. In this approach the pharmacognosists make their contribution with their strong points: natural product isolation, separation and identification, from low molecular weight compounds to macromolecules, including their expertise in biosynthesis of such compounds.

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